Status of Claims

Claims 1-11 and 22-29 are pending in the application. Claims 1-11 and 22-29 have been rejected.

Double Patenting Rejections

In the Office Action, the Examiner rejected claims 1-11 and 22-29 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-18 of issued U.S. Patent No. 5,965,130. In response, Applicants will consider, upon an indication by the Examiner of allowable subject matter, the filing of a terminal disclaimer for the above-identified U.S. Patent Application. Accordingly, Applicants respectfully request the Examiner hold the rejection in abeyance until such time.

In the Office Action, the Examiner rejected claims 1-11 and 22-29 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-10 of issued U.S. Patent No. 5,562,902. In response, Applicants will consider, upon an indication by the Examiner of allowable subject matter, the filing of a terminal disclaimer for the above-identified U.S. Patent Application. Accordingly, Applicants respectfully request the Examiner hold the rejection in abeyance until such time.

CLAIM REJECTIONS

35 U.S.C. § 112

Applicants thank the Examiner for withdrawing his rejection of claims 1-3 and 7-11 and 25-29 under 35 C.F.R §102(b), and noting that none of the cited prior art anticipates the use of IVIG for inhibiting metastasis of lymphoma.

In the Office Action, the Examiner rejected claims 1-11 and 22-29 under 35 U.S.C. § 112, as allegedly lacking support in the specification at the time of filing by containing subject matter which was not described in the specification in such a way as to convey to one skilled in the relevant art that the inventors, at the time of the application was filed, had possession of the claimed invention. Specifcally, the Examiner alleged the assertion in the specification (Page 2, lines 6-8), that lymphoma, among certain other types of cancer, is "particulary prone to metastasize", does not support claims directed to inhibiting active metastasis. Applicants respectfully disagree.

Applicants submit that throughout the Application, such as, for example, on page 7, lines 11-13 and 15-20 of the specification, Applicants provide support for treating metastasis, and lymphoma is specifically relevant in this context as it is a cancer, which metastasizes.

Moreover, Applicants submit that Examples 1-5 demonstrate a direct effect of IVIG in inhibiting metastasis of two different cancers, a carcinoma and a sarcoma, establishing therefore, support for treating cancer metastasis, as a general principle, with IVIG.

Specifically, the inhibition of metastasized cells seeding of secondary sites was demonstrated in Example 1 (see page 9, lines 29-30) and in Example 4, (page 14, lines 20-26), where the metastasized cells arose from two different cancers, and secondary seeding sites were in two different tissues (lung and liver). Applicants therefore assert that claims to IVIG inhibition of cancer metastases is supported by the specification.

Applicants submit that MPEP §2164.02 notes that sufficient support for a claimed genus (treatment of cancer metastasis with IVIG) exists, if the Specification contains representative examples (Examples 1-5), together with a statement applicable to the genus as a whole (Page 1, lines 2-4; page 3, lines 15-17 and 19), if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation.

The specification gives considerable direction and guidance (Examples 1-5), a high level of skill in the art existed at the time the application was filed and all of the methods needed to practice the invention were well known and in addition, working examples exist in the specifications (see e.g. *In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1403-07).

Further, the specification (Example 8) demonstrated that lymphoma cells are responsive to Intravenous Imuunoglobulins (IVIG) (Page 19, lines 1-2), inhibiting cell proliferation, providing further support for the applicability of the instant invention, that of preventing metastasis, to lymphoma.

In view of the above, Applicants submit that sufficient support exists for claims directed to inhibiting or treating metastastatic lymphoma in a mammal which comprises administering to the mammal a preparation of IVIG. Accordingly, Applicants request withdrawal of the 112 rejection.

The Examiner has also alleged, in this context, that one skilled in the art, based on the cited prior art, would treat primary lymphoma with IVIG, and would also therefore treat metastasis with IVIG. Applicants respectfully disagree.

One skilled in the art will readily recognize that cancerous cells that metastasize, are phenotypically distinct from cells that remain at the primary tumor site. These phenotypic differences may be evidenced in various ways, and may include up- and down-regulation of, *inter-alia*, specific adhesion molecules, matrix degradative enzymes, and response to chemotherapeutics.

For example, down regulation of adhesion molecules in metastatic cancer cells is a well-known phenomenon in the art (see e.g. Frixen et al., J. Cell Bio., Volume I 13, Number 1, April 1991 173-185, which demonstrated that E-cadherin expression is downregulated as a function of cancer cell invasiveness.; and Wang et al., Can. Res. 59, 2989-2994 at 2989 (1999), which demonstrated that while Heparan sulfate interacting protein (HIP), an adhesion

molecule, is upregulated in primary tumors, its expression is downregulated in metastasized cells).

It is also well known that metastatic cancer cells upregulate expression of matrix degradative enzymes, as compared to cells at the primary site (see e.g. John L. Herrmann, Molecular Biology of the Cell, Vol. 4, 1205-1216, November 1993, which demonstrates that enhancement of basement membrane invasion and secretion of matrix-degrading enzymes is a function of metastasis; and E. J. Bernhard, Proc. Natl. Acad. Sci. USA Vol. 91, pp. 4293-4297, May 1994 Cell Biology, which demonstrated that MMP-9 expression promotes metastasis).

Metastasized cancer cells do not respond to the same chemotherapeutics as cells at the primary tumor site (See e.g. Yen Wc et al., Pharm. Res. 1996 Sep;13(9):1305-12), which demonstrates reduced taxol sensitivity in metastatic prostate tumor cells; and Peter C. Brooks et al., J. Cell Bio., Volume 122, Number 6, September 1993 1351-1359, which demonstrated monoclonal antibodies, which are capable of inhibiting metastasis but have no effect on the primary human epidermoid carcinoma).

It would therefore not be obvious or expected that metastasized cancerous cells, which are phenotypically distinct from cells that remain at the primary site, will respond to the same therapy regimen (in this case, IVIG) as cells at the primary site.

Moreover, Applicants disagree with the Examiner's contention that IVIG treatment of primary lymphoma is known in the art. The Examiner alleged that Chapel et al., Morell et al., and Besa et al., demonstrated IVIG utility in treating primary lymphoma, and Applicant's invention lies in the distinction that IVIG is useful in treating metastasis.

Chapel et al., does not demonstrate or describe the effect the use of Intravenous Immunoglobulins in treating primary lymphoma. Chapel instead describes the use of

intravenous immunolglobulins in treating complications arising from immunocompromise (page 366, col. 1 para. 2 of the introduction, specifically):

> "since patients with B-cell malignancy and secondary hypogammaglobulinemia experience infections similar to those of patients with primary hypogammaglobilnemia, they would be expected to respond to IVIgG replacement therapy in the same way".

Specifically, Chapel concludes (page 368 last sentence of the discussion) that the discovery relates to the fact:

> "that patients of any age, with a stable disease, a history of recurrent bacterial infections and hypogammaglobulinemia should benefit from long term prophylaxis with IVIgG ".

Chapel does not describe effects of IVIgG on tumor cells, but rather on the immune system, which has been compromised by, *inter-alia* the presence of the tumor and/or its treatment with chemotherapy. There is no description or demonstration therefore in Chapel for use of IVIG in treating lymphoma, certainly not in treating metastasis of lymphoma.

Similarly, Morell et al., does not demonstrate or describe direct effects of IVIG on lymphoma. Morel reviews various treatment regimens in use for treating **secondary immunodeficiencies** associated with neoplasia, **for prevention of consequent infections**. Morell states: (last paragraph of the introduction section of page S88):

> "The following sections of this review will focus on the **treatment of secondary immunodificiencies** in tumor patients with IVIG"

Morell does not attribute IVIG to having any effect on treating lymphoma, but rather on treating symptoms associated with lymphoma. Morell reports results in terms of the frequency and severity of bacterial, fungal and viral infections contracted by patients while undergoing IVIG therapy. There is no description or demonstration in Morell et al., for use of IVIG in treating lymphoma, certainly not in treating metastasis of lymphoma.

Besa et al., does not demonstrate or describe any direct effect of Intravenous Immunoglobulins (IVIG) on primary lymphoma. Besa describe the use of IVIG for treating anemia in patients with or other related conditions producing anemia. Besa describes IVIG utility in clearing IgG-sensitized red blood cells. Besa does not provide any basis for any direct effects of IVIG on neoplastic cells, neither at a primary site, nor once metastasized.

Similar to Morrell and Chapel, Besa attributes IVIG utility in terms of affecting side effects of lymphoma, and not in terms of treating lymphoma. There is no description or demonstration in Besa, for use of IVIG in treating lymphoma, there is certainly not in treating metastasis of lymphoma.

None of the art cited suggests a direct effect of IVIG on primary tumor cells, certainly not in affecting metastasized cells, a population which is phenotypically distinct from primary cancer cells.

Accordingly, Applicants respectfully request that the rejection of claims 1-11 and 22-29 under 35 USC 112, be withdrawn.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this response, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 05-0649.

Respectfully submitted,

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